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CONTRACTING ORGANIZATION: University of Pennsylvania
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13. ABSTRACT *(Maximum 200 words)*

This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™. The recent discovery of two other natural products, epothilone and discodermolide, that operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach using synthetic and computational studies for the elucidation of the pharmacophore common to these structurally dissimilar substances. Such an advance could lead to the development of a novel family of breast cancer chemotherapeutics.

We describe herein the synthesis and biological evaluation of novel analogs of the potent antitumor agent epothilone. Our results indicate that these partial structures do not have sufficient similarity to the natural product for biological activity.

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FOREWORD

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9-19-99

PI - Signature　　　　Date

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INTRODUCTION

This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™. The recent discovery of two other natural products, epothilone and discodermolide, that operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach using synthetic and computational studies for the elucidation of the pharmacophore common to these structurally dissimilar substances. Such an advance could lead to the development of a novel family of breast cancer chemotherapeutics.

BODY

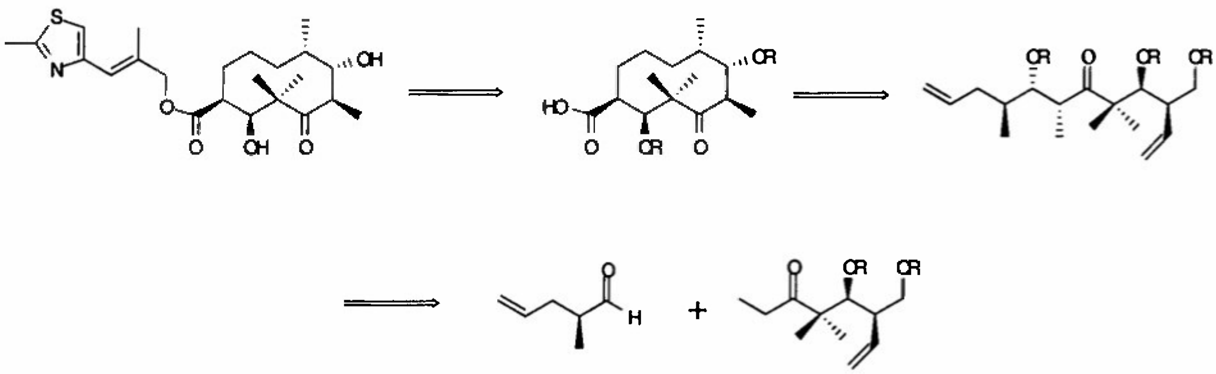
Significant progress has been achieved in realizing the first three tasks in the approved Statement of Work.

Task 1. The synthesis of both left- and right-hand halves of epothilone has been achieved.[1] The synthetic pathways are outlined explicitly in the attached publication.

Task 2..While these analogs were designed using CHARMM, we have subsequently determined that the eleven-membered ring right-hand analog does not mimic the structure of the natural product, as determined by overlaying the crystal structure of the eleven-membered ring analog (left) with epothilone (right; analog in orange).

We have applied MacroModel to a considerably more extensive conformational search and have determined that a ten-membered ring analog should overlay well with epothilone. As indicated below, the ten-membered ring analog on the left overlays well with epothilone on the right (analog shown in red).

The retrosynthetic scheme for the preparation of the new analog is shown below (unpublished; the synthetic work is really an extension of task 1). The X-ray structure of the new ten-membered ring analog does indeed overlay well onto the right-hand "hot-spot" of epothilone.



Task 3 Biological evaluation of these new compounds in the laboratory of Dr. Susan Horwitz (Abert Einstein College of Medicine, a world reknowned expert in tubulin biochemistry) revealed that none of them have biological activity, either cytotoxic activity or tubulin polymerization activity.

Relevance to the Original Hypothesis: The lack of biological activity in the new analogs that we have prepared indicates that the partial epothilone structures designed to date do not contain enough of the functionality and/or hydrophobicity of the natural product for biological activity. We are now in the process or refining the modelling for epothilone so that rationally designed new analogs can be prepared.

KEY RESEARCH ACCOMPLISHMENTS:

* New analogs of the potent antitumor substance epothilone have been prepared
* We have established that Macromodel is a superior modelling package for the evaluation of the conformational flexiblity of these novel structures; and
* Biological evaluation of these new compounds (cytotoxicity and tubulin polymerization) indicates that they are NOT biologically active.

REPORTABLE OUTCOMES:

A publication has appeared in print describing the first generation left- and right- hand analog synthesis of epothilone;

Joanne Holland has obtained a Ph.D. degree and Jiri Kasparec has obtained an M.S. degree during the course of the research;

Joanne Holland is now a research scientist at Sepracor and Jiri Kasparec is a Research Associate at Dupont Pharmaceuticals.

CONCLUSIONS:

We have established that the originally proposed partial structures of epothilone are not sufficient for the biological activity of the natural product. Modification of these structures is being pursued to achieve greater congruence with the natural product, i.e., increased

hydrophobicity. The preparation of truncated analogs with biological acitivity would represent an important advance that could be used for the refinement of the requisite SAR for the pharmacophore model. As stated previously, the development of such a model would provide the basis for the development of a new family of breast cancer chemotherapeutic agents.

REFERENCES:

[1]. Winkler, J. Holland, J. Kasparec, and P. Axelsen, "Synthesis and Biological Evaluation of Constrained Epothilone Analogs: The Efficient Synthesis of Eleven-Membered Rings by Olefin Metathesis," *Tetrahedron* (invited contribution to Symposium-in-Print on Olefin Metathesis in Synthesis) **1999** , *55*, 8199-8214.

APPENDICES:

Reference 1 and a current cv for the PI.

CURRICULUM VITAE

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EDUCATION:

Post-doctoral: Columbia University. January 1982-August 1983.
Research Director: Professor Ronald Breslow.

Graduate: Columbia University. September 1977-December 1981.
M.A. 1978, M.Phil., Ph.D. 1981.
Thesis Advisor: Professor Gilbert Stork.

Undergraduate: Harvard College. September 1973-June 1977.
A. B. cum laude in Chemistry, 1977.

PROFESSIONAL EXPERIENCE:

Professor, University of Pennsylvania
Department of Chemistry, July 1996-

Founding Member, University of Pennsylvania
Center for Cancer Pharmacology, May 1998-present

Associate Professor, University of Pennsylvania,
Department of Chemistry, July 1990-June 1996
Member, University of Pennsylvania Cancer Center,
July 1993-present

Assistant Professor, University of Chicago,
Department of Chemistry, September 1983-June 1990

AWARDS & HONORS:

American Chemical Society Cope Scholar Award, 2000
Parke-Davis Lecturer, Michigan State University, 2000
Chairman, Philadelphia Organic Chemists' Club, 1995
H. Martin Friedmann Lecturer, Rutgers University, 1993
American Cyanamid Young Faculty Award, 1989-1992
NIH-NCI Research Career Development Award, 1988-1993
Alfred P. Sloan Research Fellow, 1987-1989
Merck Foundation Award for Faculty Development, 1985
American Cancer Society Postdoctoral Fellow, 1982-1983

RESEARCH SUPPORT

ACTIVE

CA 40250-08A2 (Winkler) 2/5/98-12/31/00 20%
National Institutes of Health $191,555 (direct costs/year)
Strategies for the Synthesis of Antitumor Compounds
This proposal is directed towards the development of new approaches to the construction of the naturally occurring substances manzamine and ingenol.

N-00014-93-1-0836 (Winkler) 10/1/95-9/30/99 5%
Office of Naval Research $85,513 (direct costs/year)
Binding and Transport of Metal Ions
This proposal is directed towards the development of immobilized and fluorescent systems for the development of metal ion sensors for use in the marine environment.

BCRP-971965 (Winkler) 7/15/98-7/14/01 20%
DOD Breast Cancer Research Program (IDEA) $69,905 (direct costs/year)
Design and Synthesis of New Breast Cancer Chemotherapeutic Agents
This proposal is directed towards design and synthesis of new breast cancer chemotherapeutic agents based on taxol and epothilone. The synthetic work in this proposal is directed towards the synthesis of bicyclic analogs of epothilone

PRF-AC (33255) (Winkler) 9/01/98-8/31/00 5%
Petroleum Research Fund $30,000 (direct costs/year)
Novel Chemical Systems Based on Spiropyran Indolines
This proposal is directed towards the development of spiropyrans as control mechanisms for the design and synthesis of gating mechanisms for signal transduction, a critical component in the construction of molecular devices.

PC970475 (Winkler) 9/1/98-2/28/01 20%
DOD Prostate Cancer Research Program $114,960 (direct costs/year)
Design and Synthesis of New Prostate Cancer Chemotherapeutic Agents
This proposal is directed towards design and synthesis of new prostate cancer chemotherapeutic agents based on taxol and epothilone. The synthetic work in the DOD PC grant is directed towards the synthesis of the left- and right-hand halves of an X-ray based bridged bicylic analog of epothilone

Boehringer Ingelheim 1/1/99-12/31/99 (0%)
Synthesis of α-Methyl-α-Amino Acids $37,670 (direct costs/year)
This proposal involves support for one postdoctoral on a project that is directed towards a novel approach to the synthesis of amino acids.

PROFESSIONAL ACTIVITIES

Consultant, Wyeth-Ayerst Pharmaceuticals (1998-)
Associate Editor, *Organic Letters* (1999-)

INVITED LECTURES SINCE 1990:

Merck, Sharp & Dohme (West Point, PA)
Smith, Kline and Beckmann
Invited Lecturer, Symposium on Organic Synthesis, Great Lakes Regional ACS Meeting, Dekalb, Illinois Invited Lecturer, Molecular Recognition Meeting, Office of Naval Research, Charleston, S.C
Invited Lecturer, Symposium on Heterocyclic Chemistry, National ACS Meeting, Washington, D.C
Squibb Institute for Medical Research (Princeton, NJ)
University of Rochester
Squibb Institute for Medical Research (New Brunswick, NJ)
Boehringer-Ingelheim Pharmaceuticals
Brandeis University
University of Delaware
ICI Pharmaceuticals
New York Academy of Sciences
North Jersey ACS Meeting
Invited Lecture, 1992 Meeting of the American Society for Photobiology
Organizer and Lecturer, Symposium on Studies Toward the Total Synthesis of Taxol, National ACS Meeting, San Francisco, CA. (April 8, 1992)
Dupont Agricultural Products
Burroughs Wellcome
University of Virginia
Sandoz Institute
Sterling Winthrop
Bryn Mawr College
Invited Lecturer, Symposium on Organic Chemistry, Great Lakes Regional ACS Meeting, Ann Arbor, Michigan
Invited Lecturer, Symposium on Organic Synthesis, Middle Atlantic Regional ACS Meeting, Baltimore, Maryland
Technion-Israel Institute of Technology
Pfizer Central Research
Sandoz Institute
Hebrew University of Jerusalem
R. W. Johnson
University of Montreal
Plenary Lecturer, Wyeth-Ayerst Fourth Annual Chemical Sciences Symposium
Merck (West Point, PA)
American Cyanamid
Rhone-Poulenc Agricultural
Plenary Lecture, Interamerican Photochemical Society
University of Maryland
R. W. Johnson Pharmaceutical Research
Wyeth-Ayerst
Sepracor

Boehringer-Ingelheim
Florida State University
Northwestern University
UCLA
University of Minnesota
Parke-Davis
Pfizer
Penn State University
Smith Kline Beecham
Temple University
Amgen
University of Chicago
Dupont Pharmaceuticals
Invited Speaker, Symposium on Solid Support Chemistry, Middle Atlantic Regional ACS Meeting, May 1999
Plenary Lecturer, Symposium on Heterocycles, Canadian Institute of Chemistry, June 1999
Invited Speaker, Gordon Conference on Heterocycles, July 2000
University of Western Ontario
Boehringer-Ingelheim, Montreal
Michigan State University

PUBLICATIONS :

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TETRAHEDRON

Design and Synthesis of Constrained Epothilone Analogs: The Efficient Synthesis of Eleven-Membered Rings by Olefin Metathesis

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Abstract: The efficient synthesis of both left- and right-hand halves of a constrained analog of the anticancer natural product epothilone is described. The eleven-membered rings common to both compounds are prepared by olefin metathesis.

Keywords: *Metathesis, biologically active compounds, antitumour compounds.*

Introduction

The discovery of Taxol™ (paclitaxel) **1** has been an important breakthrough in cancer chemotherapy because of its remarkable clinical efficacy against breast and ovarian cancer. In addition, its activity involves an entirely different mechanism of action from conventional cancer chemotherapies.[1] Until recently, Taxol™ was the only compound known to promote the assembly of microtubules and inhibit the tubulin disassembly process.[2] However, three natural products of very different structural types, epothilone **2**,[3] eleutherobin **3**,[4] and discodermolide **4** [5] have recently been found to operate by a similar mechanism of action. These recent disclosures provide an important stimulus to investigate the functional similarities of these substances. The identification of the pharmacophore of these structurally dissimilar substances could lead to the development of a novel family of chemotherapeutic agents that operate in a Taxol™-like manner, but without the multi-drug resistance, solubility or formulation problems that have limited the success of Taxol™ in cancer chemotherapy. Towards that end, we describe herein the synthesis and biological evaluation of novel eleven-membered ring analogs of epothilone that have been designed to aid in the identification of the Taxol™/epothilone pharmacophore. The synthetic routes employed feature the first examples of the Grubbs metathesis reaction as a highly efficient method for the preparation of eleven-membered rings.

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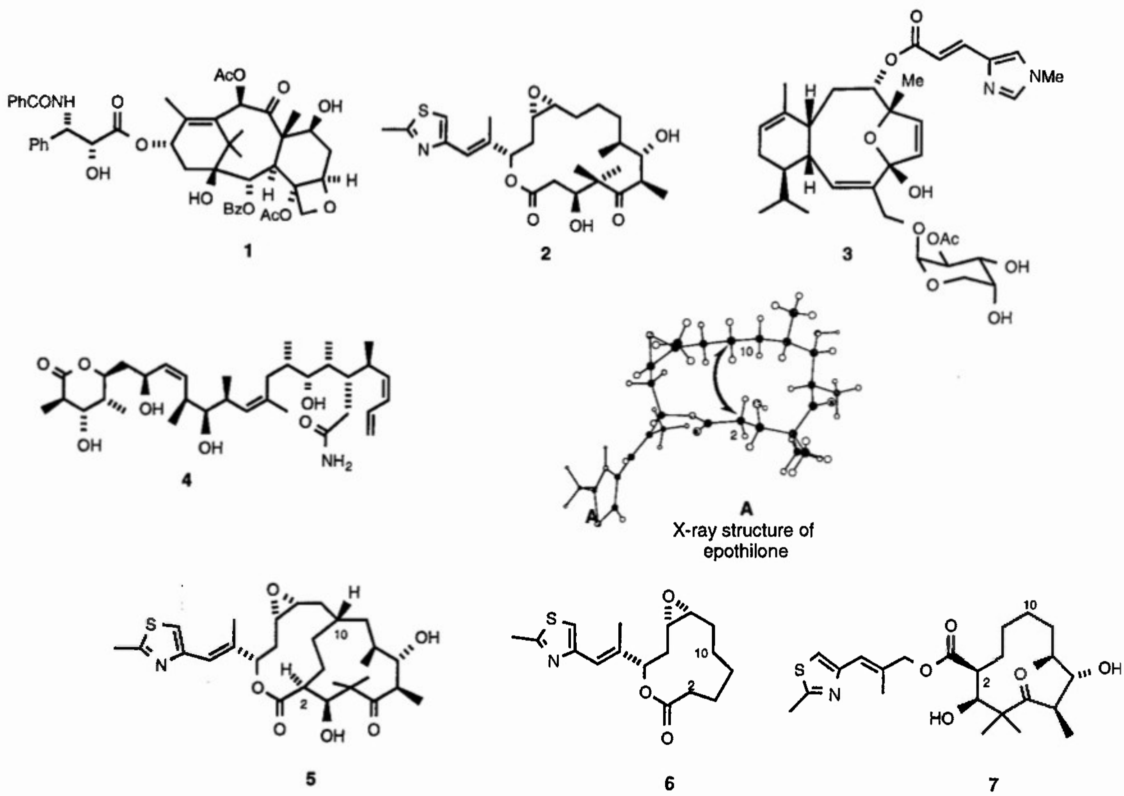
Results

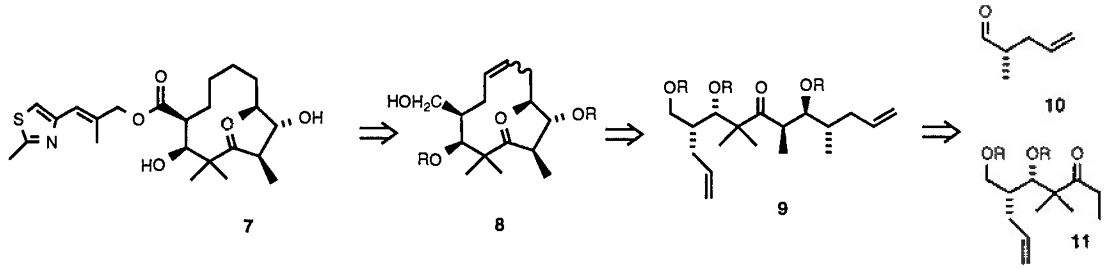
We have designed a constrained analog of epothilone based on the X-ray conformation of **2** as shown in **A**.[6] The two carbon transannular tether from C2 to C10 of epothilone, as indicated with the arrows in **A**, serves to simultaneously rigidify and partition epothilone as shown in **5**. This new compound leads to the separation of the left and right halves of the epothilone molecule and permits, for the first time, the biological evaluation of the separated halves of epothilone. The thiazole sidechain of epothilone has been included on both the left- and right-half analogs **6** and **7** to mimic the structure of the natural product as closely as possible. The reported total syntheses of epothilone **2** [7-9] have made available the technology for the synthesis of diverse analogs of the parent structure and such efforts have recently been disclosed from the laboratories of Danishefsky [10] and Nicolaou.[11] Using closely related approaches, we have prepared **6** and **7** in which both eleven-membered rings are prepared by olefin metathesis as outlined in the Schemes below.

Scheme 1



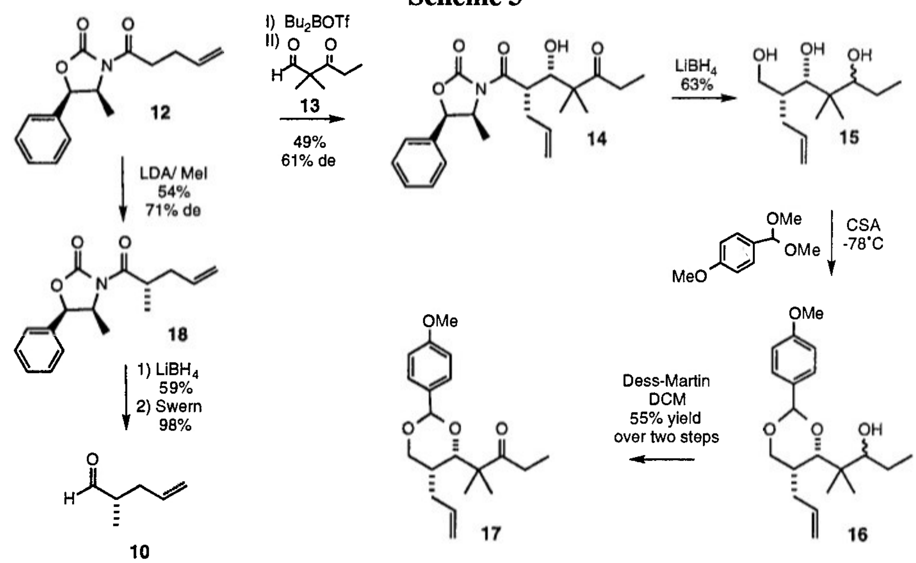
The cycloundecane carboxylic acid ester **7** could be sequentially derived by alkene reduction, alcohol oxidation and esterification of **8**, which would in turn be prepared by eleven membered ring-forming olefin metathesis of **9**. The intermediacy of the cycloundecene **8** would permit the evaluation of both saturated and unsaturated analogs of the eastern hemisphere of epothilone. We envisioned that **9** could be prepared by the aldol reaction of **10** and **11**, using the β-ketol stereochemistry in **11** to control the asymmetric induction in the aldol reaction.

Scheme 2

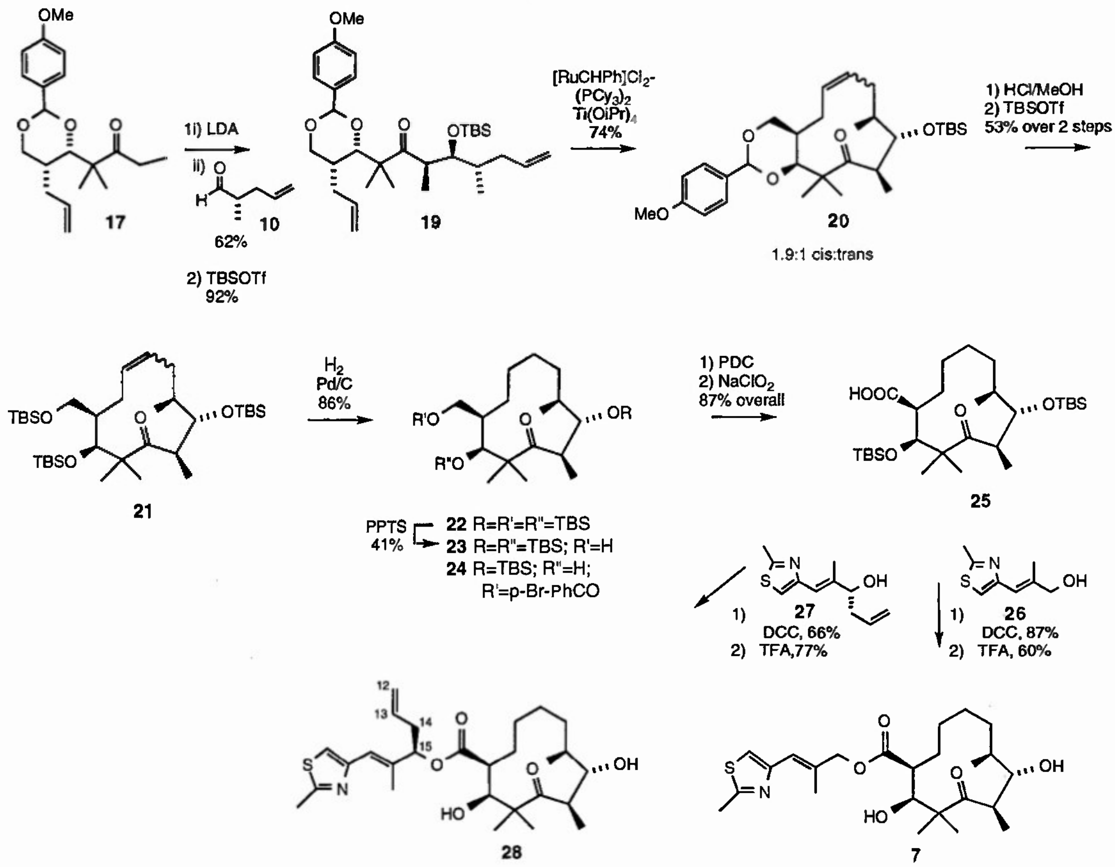


The synthesis of ethyl ketone **17** (corresponding to **11**) is outlined in Scheme 3. Reaction of the boron enolate derived from the pentenoylated Evans oxazolidinone **12** [12a] with ketoaldehyde **13** gave **14**. Reduction of **14** gave triol **15**, which was condensed with anisaldehyde dimethyl acetal to give secondary alcohol acetal **16** [accompanied by the primary alcohol acetal (not shown)], which on oxidation gave **17**. The requisite aldehyde **10** could be prepared from oxazolidinone **12** by methylation, reduction and oxidation as shown in Scheme 3.[12b,c]

Scheme 3



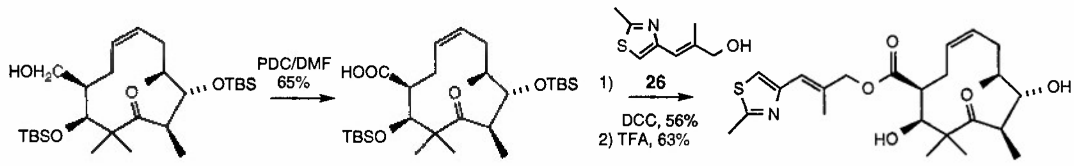
Scheme 4



Aldol condensation of **17** and **10** (Scheme 4) led to the selective formation of a major diastereomer (11:1), which, after silylation, was assigned the relative stereochemistry shown in **19**, based on the work of Schinzer and subsequently confirmed by X-ray crystal structure analysis. Reaction of the olefin metathesis substrate **19** with the Grubbs catalyst [13] in the presence of $Ti(OiPr)_4$ gave the cycloundecene **20** as a 1.9:1 mixture of double bond isomers [J=10.8 Hz for *cis* (major); J=15.1 Hz for *trans* (minor)] in 74% yield. The use of $Ti(OiPr)_4$ to prevent chelation of heteroatom functionalities in **19** to the metallocarbene intermediate was first described by Fürstner and is critical to the success of this reaction.[14] Only recovered starting material was observed in this reaction in the absence of the Lewis acid at the same concentration of substrate. Hydrolysis of the benzylidene acetal in **20** followed by exhaustive silylation gave **21**. Reduction of the mixture of alkenes gave a single product **22**, which on treatment with pyridinium tosylate in methanol led to the selective removal of the primary TBS group to give **23**. Alternatively, hydrolysis of the benzylidene acetal **20**, followed by hydrogenation of the cycloundecene, and p-bromobenzoylation of the primary alcohol gave **24**,

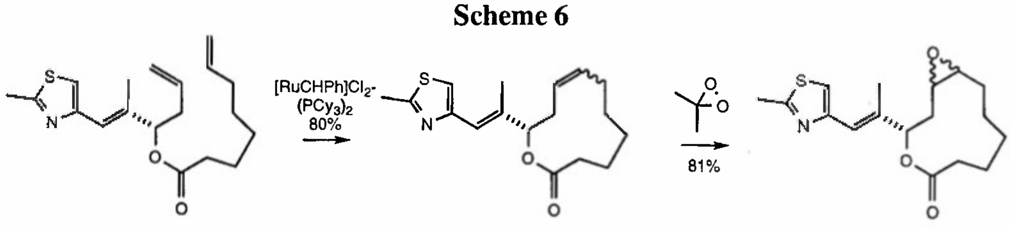
which provided crystals suitable for X-ray crystallographic analysis, thereby confirming the stereochemical relationships as shown in **24**. Oxidation of **23** with PDC gave the corresponding aldehyde, which on reaction with sodium chlorate gave the acid **25**. Esterification with the thiazole allylic alcohol **26**,[15] followed by desilylation gave the target compound **7**. In an effort to more closely mimic the hydrophobicity of epothilone, acid **25** was also esterified with **27** and desilylated to give **28**, with the correct absolute stereochemistry at C-15 and containing all but one of the carbon atoms of epothilone. Careful hydrolysis of **20** with CSA in methanol/dichloromethane led to the isolation of a pure sample of the cis-alkene primary alcohol **29** (Scheme 5).[16] Oxidation of the primary alcohol **29** with PDC gave **30**, which on esterification with **26** and desilylation gave **31**.

Scheme 5



The synthesis of **6**, the "left-hand" half of **5**, is outlined in Scheme 6. Esterification of **27** with 7-octenoic acid (DCC, 70%) led to the formation of the olefin metathesis substrate **32**, which on reaction with the Grubbs catalyst gave the eleven-membered ring **33** as a separable 1:1 mixture of alkene stereoisomers (*J*=10.2 Hz for *cis*; *J*=15.6 Hz for *trans*). Epoxidation of each of the separated *cis* and *trans* stereoisomers of **33** led to the formation of a 1:1 mixture of stereoisomeric epoxides **6**, which could not be separated by chromatography and were evaluated as a mixture of isomers.

Scheme 6



Biological Results

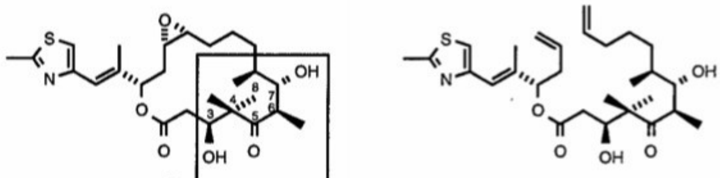
Preliminary evaluation of **6**, **7**, **28**, **31** and both cis and trans-**33** by Dr. Susan Horwitz revealed that none of these simple analogs of epothilone bind tubulin at concentrations up to 20 μM.

Discussion

The Grubbs metathesis reaction is a powerful method for the synthesis of a large variety of carbocyclic ring systems.[17] The relative thermodynamic instability of medium-size rings has made their derivatives relatively difficult to obtain,[18] even by olefin metathesis.[19] We have described the first examples of the application of the Grubbs metathesis reaction to the efficient synthesis (74% yield for **20** and 80% yield for **33**) of eleven-membered rings, in which the medium ring products are prepared from acyclic precursors. The highly functionalized substrate **20** enjoys the additional benefit of the acetal moiety which serves to constrain degrees of freedom in the metathesis substrate. In accord with the observations of Fürstner, we have observed the critical role of a Lewis acid for the success of the metathesis reaction of highly heteroatom-substituted substrates by preventing unproductive chelation of the metallocarbene intermediate to the heteroatom functionality.

Epothilone is the first naturally occurring compound whose biological profile resembles that of the clinically important anticancer agent Taxol™. Work by Bollag and co-workers at Merck suggests that epothilone binds to the same site on microtubules as does Taxol™.[20] The establishment of the pharmacophore common to these two structurally dissimilar substances could therefore lead to a new family of cancer chemotherapeutic agents.[21] A considerable body of SAR data for epothilone, with respect to both cytotoxicity and tubulin binding, has recently emerged from the laboratories of Danishefsky [10] and Nicolaou.[11]

Scheme 7

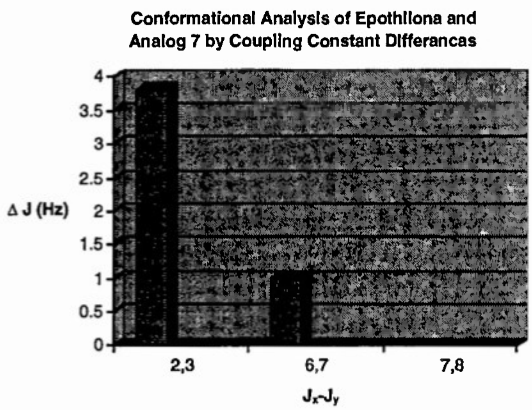


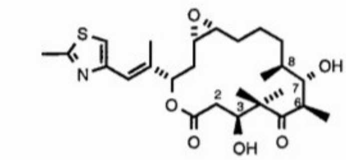
34 **35**

Danishefsky and co-workers have proposed a "hot spot" for epothilone from C-3 to C-8 as shown in **34**. We have reported herein the preparation of a series of eleven-membered ring analogs of epothilone, **7**, **28** and **31**, that contains the "hot spot" functionality. However, the activities of these compounds, at concentrations up to 20 μM, are not significant, suggesting that the "hot spot" alone is not sufficient for biological activity. This conclusion is supported by the recent findings of Nicolaou and Danishefsky regarding the intolerance of other macrocyclic ring sizes in epothilone analogs.[10, 22] Even with addition of all but one of the carbons present in the natural product **2**, i.e., **28**, no activity was observed, a result that points to the importance of the macrocyclic ring and the apparent uniqueness of the sixteen-membered ring of epothilone. The lack of activity observed for **6** and **33** is somewhat less surprising based on the importance that has been attributed to the C-3 to C-8 domain of epothilone [10].

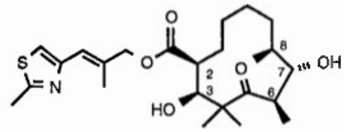
Preliminary MacroModel calculations on both epothilone **2** and the analogs that we have prepared, i.e., **7**, indicate that a plethora of conformers exist in close energetic proximity, making a more quantitative analysis of this problem exceedingly difficult. However, comparison of the ^{1}H NMR coupling constants of **2** and **7** permits the evaluation of the similarities of the time-averaged conformations of epothilone and the eleven-membered ring analogs.[23] As shown in the Table below, the differences between the *J* values for H-2/H-3 in **2** and in **7** are much greater than those from H-6 to H-8 in **2** and in **7**, suggesting greater congruence of analog **7** with the natural product **2** in that region. This similarity, however, is clearly not sufficient for biological activity, based on the data outlined above.

Table





2



7

Conclusions

We have established that the Grubbs metathesis reaction affords a uniquely efficient approach to the synthesis of eleven-membered rings. Preliminary biological data for the compounds that we have prepared points to the critical importance of the sixteen-membered ring of epothilone. The synthesis of constrained epothilone analogs based on the apparently critical sixteen-membered ring, i.e., **5** (Scheme 1), is currently underway and our results will be reported in due course.

Experimental

Aldol Adduct 14: To a solution of pentenoylated oxazolidone **12** (40.723 g, 0.157 mol) in methylene chloride (319 mL) at 0°C was added dibutylborontriflate (146 mL, 1.0 M in methylene chloride, 0.146 mol) followed by freshly distilled triethylamine (26.611 mL, 0.191 mol) extremely slowly so as to prevent the internal temperature from rising above 3°C. The resulting pale yellow solution was cooled to -78°C before adding aldehyde **13** (14.375 g, 0.112 mol) in methylene chloride (6 mL) slowly. The resulting solution was allowed to

continue stirring at this temperature for 10 minutes before warming to 0°C and stirring for three hours. The reaction was then quenched by the addition of pH 7 aqueous phosphate buffer followed by methanol, all at a rate so as to keep the internal temperature below 10°C. Next, a 2:1 solution of methanol:30% aqueous hydrogen peroxide was added slowly, again maintaining the reaction temperature below 10°C, and the resulting mixture then allowed to warm to room temperature and stir for one hour. The volatile material was then removed *in vacuo* and the resulting mixture extracted with diethyl ether. The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate followed by brine, dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 5% to 50% ethyl acetate-petroleum ether to give the desired aldol adduct **14** (21.126 g, 49%; 65% based on recovered starting acylated oxazolidinone). [α] -12.7° (c 1.00, $CHCl_3$); IR (neat) 3498, 1780, 1697, 1343, 1195 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.41 (m, 3 H), 7.28–7.29 (m, 2 H), 5.77-5.85 (m, 1 H), 5.68 (d, 1 H, J = 7.3 Hz), 4.95-5.02 (m, 2 H), 4.71 (quintet, 1 H, J = 6.9 Hz), 4.24 (q, 1 H, J = 6.5 Hz), 4.13 (t, 1 H, J = 6.5 Hz), 3.00 (d, 1 H, J = 6.6 Hz), 2.56 (q, 2 H, J = 7.3 Hz), 2.48 (t, 2 H, J = 7.2 Hz), 1.23 (s, 3 H), 1.17 (s, 3 H), 1.02 (t, 3 H, J = 7.1 Hz), 0.82 (d, 3 H, J = 6.6 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 217.4, 175.0, 152.8, 134.9, 133.3, 128.8, 128.7, 125.7, 117.4, 78.8, 76.4, 55.1, 51.8, 44.1, 34.2, 31.5, 21.9, 21.4, 14.6, 7.8. HRMS calculated for $C_{22}H_{29}NO_5$: ($M+NH_4$) 405.2389; found: 405.2394.

Triol 15: To a solution of aldol adduct **14** (870 mg, 2.25 mmol) in diethyl ether (44 mL) was added water (89 µL, 4.95 mmol) and the solution cooled to 0°C. Lithium borohydride (2.5 mL, 2.0 M in tetrahydrofuran, 4.95 mmol) was then added dropwise and the resulting milky mixture stirred for one hour at 0°C followed by three hours at room temperature. The reaction was then quenched by the addition of 1M NaOH and the mixture stirred until both layers became clear. The organic layer was then separated and the aqueous layer further extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 40% to 60% ethyl acetate-petroleum ether to give the desired triol **15** (309 mg, 63%) as a 2.3:1 mixture of diastereomers. IR (neat): 3344, 1640, 1470 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.77–5.85 (m, 1 H), 4.98-5.07 (m, 2 H), 3.85-3.86 (m, 1 H), 3.60-3.76 (m, 4 H), 3.33-3.45 (m, 1 H), 3.11 (br s, 0.7 H), 2.76 (br s, 0.3 H), 2.37-2.40 (m, 0.3 H), 2.29-2.34 (m, 0.7 H), 2.11-2.21 (m, 1 H), 1.79-1.82 (m, 0.7 H), 1.68-1.72 (m, 0.3 H), 1.52-1.57 (m, 1 H), 1.35-1.42 (m, 0.3 H), 1.26-1.34 (m, 0.7 H), 0.98 (t, 0.9 H, J = 7.3 Hz), 0.96 (t, 2.1 H, J = 7.3 Hz), 0.95 (s, 0.9 H), 0.94 (s, 2.1 H), 0.88 (s, 0.9 H), 0.77 (s, 2.1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 137.7, 137.5, 116.0, 115.9, 82.5, 81.7, 81.1, 80.1, 66.0, 65.8, 41.7, 41.0, 40.4, 40.3, 29.8, 29.7, 24.4, 24.1, 22.0, 21.6, 21.1, 15.6, 11.4, 11.2. HRMS calculated for $C_{12}H_{24}O_3$ (M+H): 217.1803; found: 217.1809.

Benzylidine acetal 16: To a solution of triol **15** (20 mg, 0.09 mmol) in methylene chloride (1 mL) at -78°C was added anisaldehyde dimethylacetal (16 µL, 0.094 mmol) followed by catalytic camphorsulfonic acid (1 mg) and the reaction allowed to continue stirring at this temperature for one hour before quenching by the addition of a saturated aqueous solution of sodium bicarbonate. The mixture was allowed to warm to room temperature before further diluting with water and extracting with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to provide a mixture of regioisomers. Separation of the regioisomers was not accomplished, but instead the mixture was carried on to the next step.

Ethyl ketone 17: To a solution of the regioisomeric mixture of alcohols **16** (31 mg, 0.092 mmol) in methylene chloride (1 mL) at 0°C was added Dess-Martin periodinane reagent (118 mg, 0.28 mmol).[24] The reaction was then warmed to room temperature and allowed to continue stirring for 2 hours. The reaction mixture was poured into 2M NaOH and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using 10% ethyl acetate-petroleum ether to give the desired ketone **17** (15 mg, 55% for two steps). [α] -37.4° (c 0.7, $CHCl_3$); IR (neat) 1699, 1615, 1517, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, 2 H, J = 8.6 Hz), 6.89 (d, 2 H, J = 8.7 Hz), 5.67-5.77 (m, 1 H), 5.46 (s, 1 H), 5.03-5.09 (m, 2 H), 4.21 (dd, 1 H, J = 1.0, 11.4 Hz), 4.00 (d, 1 H, J = 2.1 Hz), 3.81-3.84 (m, 1 H), 3.80 (s, 3 H), 2.63 (dq, 1 H, J = 7.2, 75.4 Hz), 2.60 (dq, 1 H, J = 7.2, 75.4 Hz), 2.42-2.49 (m, 1 H), 2.15-2.18 (m, 1 H), 1.61-1.64 (m, 1 H), 1.23 (s, 3 H), 1.21 (s, 3 H), 1.00 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 215.7, 160.0, 136.4, 131.3, 127.3, 117.1, 113.6, 102.6, 85.5, 70.2, 55.3, 50.8, 35.6, 32.6, 29.2, 23.0, 21.8, 8.2. HRMS calculated for $C_{20}H_{28}O_4$ (M+H): 333.2065; found: 333.2068.

TBS ether 19: To a solution of diisopropylamine (1.1 mL, 8.3 mmol) in tetrahydrofuran (15.8 mL) at 0°C was added *n*BuLi (3.6 mL, 2.30 M in hexanes, 8.2 mmol) dropwise. The solution was allowed to stir at this temperature for ten minutes before cooling to -78°C and maintaining this temperature for several hours before use. To the LDA solution was then added a solution of benzylidene acetal ketone **17** (2.479 g, 7.5 mmol) in tetrahydrofuran (7.3 mL) dropwise and the resulting solution allowed to stir at this temperature for one hour. To the enolate solution was then added a solution of 2-methylpent-3-enal **10** (805 mg, 8.2 mmol) in tetrahydrofuran (7 mL) dropwise. The reaction was allowed to continue at -78°C for 20 minutes, quenched by the addition of a saturated aqueous solution of ammonium chloride and was then allowed to warm to room temperature. The mixture was diluted further with water and the aqueous layer extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using 10% ethyl acetate-petroleum ether to give the desired aldol adduct (1.986 g major diastereomer, 62%). [α] -24.0° (c 1.0, $CHCl_3$); IR (neat) 3497, 1680, 1639, 1616, 1517, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.6 Hz), 5.65-5.79 (m, 2H), 5.44 (s, 1H), 5.08 (dd, 2H, J = 21.2, 13.6 Hz), 4.94-4.98 (m, 2H), 4.21-4.23 (m, 1H), 4.04 (d, 1H, J = 2.1 Hz), 3.82-3.84 (m, 1H), 3.78 (s, 3H), 3.46 (s, 1H), 3.36 (q, 1H, J = 7.0 Hz), 3.23 (d, 1H, J = 9.4 Hz), 2.42-2.56 (m, 2H), 2.22-2.26 (m, 1H), 1.71-1.77 (m, 1H), 1.63-1.66 (m, 1H), 1.49-1.57 (m, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.00 (d, 3H, J = 6.9 Hz), 0.58 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 222.9, 160.0, 137.0, 136.2, 131.0, 127.3, 117.2, 116.1, 113.5, 102.6, 85.4, 74.5, 70.2, 55.2, 51.8, 41.5, 37.3, 35.7, 35.2, 29.7, 22.7, 20.5, 14.6, 9.9. HRMS calculated for $C_{26}H_{38}O_5$ (M+H): 431.2797; found: 431.2797.

To a solution of the alcohol prepared above (260 mg, 0.6 mmol) in methylene chloride (2.8 mL) at -78°C was added 2,6-lutidine (330 µL, 2.8 mmol) followed by TBSOTf (288 µL, 1.3 mmol) dropwise. The reaction was allowed to continue stirring with gradual warming to room temperature over three hours before treating with pH 7 aqueous phosphate buffer and extracting with diethyl ether. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using 5% ethyl acetate-petroleum ether to give the desired TBS ether adduct **19** (303 mg, 92%). [α] -17.6° (c 1.0, $CHCl_3$); IR

(neat): 1695, 1639, 1616, 1517, 1249 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3): δ 7.36 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 5.73-5.81 (m, 1H), 5.46-5.54 (m, 1H), 5.45 (s, 1H), 5.05-5.12 (m, 2H), 4.84-4.89 (m, 2H), 4.28 (d, 1H, J= 2.0 Hz), 4.21-4.23 (m, 1H), 3.86-3.88 (m, 1H), 3.77-3.80 (m, 1H), 3.78 (s, 3H), 3.26 (quin, 1H, *J* = 6.9 Hz), 2.55-2.62 (m, 1H), 2.33-2.35 (m, 1H), 2.08-2.13 (m, 1H), 1.65-1.74 (m, 2H), 1.33-1.39 (m, 1H), 1.31 (s, 3H), 1.22 (s, 3H), 1.06 (d, 3H, *J* = 6.9 Hz), 0.048 (s, 3H), 0.036 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl3): δ 218.4, 160.0, 137.8, 136.6, 131.3, 127.5, 117.0, 115.4, 113.5, 102.4, 83.6, 77.6, 70.5, 55.2, 51.8, 44.9, 38.2, 35.6, 35.4, 30.1, 26.2, 22.1, 21.9, 18.5, 17.6, 16.3, −3.6, −3.7. HRMS calculated for $C_{32}H_{52}O_5Si$ (M+H): 545.3662; found: 545.3674.

Cycloundecene 20: To a solution of TBS ether **19** (320 mg, 0.59 mmol) in methylene chloride (1.17 L) was added Ti(O*i*Pr4) (53 µL, 0.18 mmol, freshly fractionally distilled *in vacuo*) and the solution allowed to reflux for one hour before adding a solution of bis(tricyclohexyl-phosphine)benzylideneruthenium dichloride (48 mg, 0.059 mmol) in methylene chloride (16 mL). The reaction was allowed to continue at reflux for seven hours before allowing to cool to room temperature. The solution was then concentrated *in vacuo* and the residue purified by flash column chromatography using 5% ethyl acetate-petroleum ether to give the desired eleven-membered metathesis product **20** (225 mg, 74%) as a 1.9:1 ratio of double bond isomers. IR (neat): 1700, 1616, 1517, 1249 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3): δ 7.54 (d, 0.68H, *J* = 8.7 Hz), 7.46 (d, 1.32H, *J* = 8.7 Hz), 6.90 (d, 0.68H, *J* = 8.7 Hz), 6.88 (d, 1.32H, *J* = 8.7 Hz), 5.62-5.66 (m, 0.66H), 5.49-5.53 (m, 0.66H), 5.42 (s, 0.66H), 5.38 (s, 0.34H), 5.24-5.29 (m, 0.34H), 5.15-5.20 (m, 0.34H), 4.31-4.32 (m, 0.34H), 3.97-4.12 (m, 2.66H), 3.79 (s, 1.02H), 3.79 (s, 1.98H), 3.58 (d, 0.66H, *J* = 1.9 Hz), 3.49-3.50 (m, 0.34H), 3.40 (dq, 0.66H, *J* = 6.9, 3.7 Hz), 2.94 (dq, 0.34H, *J* = 7.4, 2.6 Hz), 2.71-2.78 (m, 0.34H), 2.34-2.46 (m, 1.66H), 1.99-2.13 (m, 2.66H), 1.84-1.85 (m, 0.66H), 1.77-1.79 (m, 0.34H), 1.66 (dt, 0.34H, *J* = 10.6, 14.1 Hz), 1.35 (s, 3H), 1.29 (s, 1.02H), 1.27 (s, 1.98H), 1.04 (d, 1.02H, *J* = 6.2 Hz), 1.03 (d, 1.98H, *J* = 6.9 Hz), 0.92 (d, 1.98H, *J* = 6.3 Hz), 0.89 (s, 5.94H), 0.85-0.89 (m, 1.02H), 0.88 (s, 3.06H), 0.12 (s, 3.96H), 0.10 (s, 1.02H), 0.10 (s, 1.02H). HRMS calculated for $C_{30}H_{47}O_5$ Si (M+Na): 539.3169; found: 539.3160.

Cycloundecene trisilyl ether 21: To a solution of benzylidene acetal **20** (56 mg, 0.11 mmol) in diethyl ether (3 mL) was added a solution of 3% HCl/MeOH (1.5 mL) and the reaction allowed to stir for 15 minutes at which time an additional portion of 3% HCl/MeOH (1.5 mL) was added. The reaction was allowed to stir for ten more minutes before concentrating *in vacuo*. The crude diol was then dissolved in methylene chloride (720 µL) and the solution cooled to -78°C before adding 2,6-lutidine (119 µL, 1.02 mmol) followed by TBSOTf (105 µL, 0.46 mmol) dropwise. The reaction was allowed to gradually warm to 0°C over two hours at which time additional TBSOTf (105 µL, 0.4 mmol) was added. The reaction was then allowed to warm to room temperature and stir for two hours. The mixture was then partitioned between pH 7 aqueous phosphate buffer and ethyl acetate, the combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using 1% ethyl acetate-petroleum ether to give the desired trisilyl ether **21** (36 mg, 53% for two steps). Selected NMR data (major isomer only): ^{1}H NMR (500 MHz, CDCl3) δ 5.44–5.59 (m, 2H), 3.95 (d, 1H, *J* = 4.9 Hz), 3.64 (s, 1H), 3.45-3.50 (m, 1H), 3.36-3.41 (m, 1H), 3.19 (quintet, 1H, *J* = 6.8 Hz), 2.24-2.32 (m, 1H), 2.13-2.18 (m, 1H); IR (neat): 1696, 1471, 1254, 1098, 836. HRMS calculated for $C_{34}H_{70}O_4Si_3$ (M+H): 627.4660; found: 627.4655.

Cycloundecane trisilyl ether 22: A solution of the mixture of *cis* and *trans* alkenes **21** (29 mg, 0.04 mmol) in 10:1 methanol/ethyl acetate (1 mL MeOH:0.1 mL EtOAc) was purged with argon for ten minutes. Next, 10% Pd/C (5 mg) was added and the mixture further purged with hydrogen gas and allowed to continue stirring under an atmosphere of hydrogen for four hours. The mixture was then filtered through celite, washed with ethyl acetate, and concentrated *in vacuo*. The residue was purified by flash column chromatography using a gradient of 1% to 10% ethyl acetate-petroleum ether to give the desired saturated eleven-membered ring **22** (25 mg, 86%). IR (neat): 1694, 1472, 1463, 1255, 1100, 835, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.95 (dd, 1H, *J* = 0, 8.4 Hz), 3.58 (d, 1H, *J* = 2.9 Hz), 3.43-3.51 (m, 2H), 3.18 (pent, 1H, *J* = 6.9 Hz), 1.95-2.01 (m, 1H), 1.62-1.68 (m, 1H), 1.39-1.58 (m, 5H), 1.30 (s, 3H), 1.24-1.27 (m, 1H), 1.17 (m, 3H), 1.12-1.15 (m, 2H), 1.05 (d, 3H, *J* = 6.9 Hz), 0.93 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87-0.88 (m, 3H), 0.070 (s, 3H), 0.054 (s, 3H), 0.041 (s, 3H), 0.034 (s, 6H), 0.0030 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 216.2, 80.5, 78.1, 64.8, 52.6, 48.0, 42.9, 36.0, 30.4, 29.4, 26.2, 26.2, 26.1, 26.0, 25.1, 25.1, 23.4, 18.9, 18.7, 18.5, 18.3, 17.9, –3.2, –3.6, –3.7, –4.2, –5.2, –5.3. HRMS calculated for $C_{34}H_{72}O_4Si_3$ (M+H): 629.4817; found: 629.4798.

Alcohol 23: To a solution of the trisilyl ether **22** (9 mg, 0.01 mmol) in methanol (0.3 mL) at 0°C was added catalytic PPTS and the reaction allowed to continue stirring at this temperature while monitoring by TLC. After 4 hours the reaction was warmed to room temperature with stirring for 18 hours. Although TLC analysis showed the reaction was not complete, the reaction was worked up after approx. 24 hours. The reaction mixture was partitioned between pH 7 aqueous phosphate buffer and ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 4% to 10% ethyl acetate-petroleum ether to give the desired primary hydroxyl **23** (3 mg, 41%; 92% based on recovered starting material). [α] -8.4° (c 0.5, $CHCl_3$); IR (neat): 3482, 1693, 1472, 1253, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.95 (dd, 1H, *J* = 1.1, 8.5 Hz), 3.60 (d, 1H, *J* = 2.9 Hz), 3.53-3.60 (m, 2H), 3.20 (dq, 1H, *J* = 6.9, 13.9 Hz), 2.02-2.05 (m, 1H), 1.55-1.66 (m, 2H), 1.40-1.50 (m, 3H), 1.33 (s, 3H), 1.11-1.29 (m, 5H), 1.19 (s, 3H), 1.06 (d, 3H, *J* = 6.9 Hz), 0.93 (s, 9H), 0.88 (s, 9H), 0.87-0.88 (m, 3H), 0.11 (s, 3H), 0.057 (s, 3H), 0.044 (s, 3H), 0.024 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 216.0, 81.1, 78.2, 64.6, 52.4, 48.0, 42.9, 35.6, 30.0, 29.5, 26.2, 26.2, 25.6, 25.2, 24.8, 23.3, 18.8, 18.7, 18.5, 18.0, –3.4, –3.6, –3.7, –3.9. HRMS calculated for $C_{28}H_{58}O_4Si_2$ (M+H): 515.3952; found: 515.3967.

X-ray Derivative 24: After hydrolysis of the benzylidene acetal (as described above for the preparation of trisilyl ether **21**), the resulting diol (29 mg, 0.07 mmol), as a mixture of *cis* and *trans* isomers, was dissolved in methanol/ethyl acetate (10:1, 2 mL methanol: 0.2 mL ethyl acetate) and the solution purged with argon for ten minutes. Next, 10% Pd/C (5 mg) was added and the mixture was purged with hydrogen gas and allowed to continue stirring under an atmosphere of hydrogen for 18 hours. The mixture was then filtered through celite, washing with ethyl acetate, and concentrated *in vacuo*. The resulting white solid (27 mg, 93%) was carried on without further purification.

To a solution of the saturated eleven-membered ring prepared above (28 mg, 0.07 mmol) in dichloromethane (0.7 mL) at 0°C was added pyridine (17 μL, 0.21 mmol) followed by *p*-bromobenzoyl chloride (38 mg, 0.18 mmol) and catalytic DMAP. The reaction was allowed to warm to room temperature with stirring for 24 hours

before diluting the reaction mixture with ethyl acetate and washing with water followed by saturated aqueous sodium bicarbonate. The organic extract was dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient 10% to 40% ethyl acetate-petroleum ether to give the desired ester **24** (10 mg, 24%; 69% based on recovered starting material). [α] +12.9° (c 0.45, $CHCl_3$); IR (neat): 3456, 1721, 1670, 1590, 1462, 1270 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83–7.87 (m, 2H), 7.53–7.57 (m, 2H), 4.32 (dd, 1H, J = 5.6, 10.7 Hz), 4.24 (dd, 1H, J = 8.8, 10.6 Hz), 4.10 (d, 1H, J = 9.0 Hz), 3.97 (dd, 1H, J = 2.2, 7.3 Hz), 3.53 (dd, 1H, J = 1.4, 9.1 Hz), 3.21 (quintet, 1H, J = 7.1 Hz), 2.02-2.04 (m, 1H), 1.51-1.70 (m, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.22-1.30 (m, 3H), 1.14 (d, 3H, J = 7.1 Hz), 1.02-1.12 (m, 3H), 0.89 (d, 3H, J = 6.5 Hz), 0.88 (s, 9H), 0.077 (s, 3H), 0.070 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 224.9, 165.7, 131.7, 131.0, 129.3, 128.0, 82.8, 76.1, 66.8, 49.2, 46.0, 40.7, 37.2, 30.2, 30.0, 29.7, 26.9, 26.8, 26.1, 22.4, 18.4, 17.6, 17.1, −3.8, −3.9. HRMS calculated for $C_{29}H_{47}BrO_5Si$ (M+Na): 605.2274; found: 605.2264.

Carboxylic acid 25: To a solution of primary alcohol **23** (10 mg, 0.02 mmol) in dimethylformamide (0.43 mL) at room temperature was added PDC (81 mg, 0.2 mmol) and the reaction allowed to stir vigorously for four hours. The reaction mixture was then partitioned between distilled water (4.0 mL) and diethyl ether. The combined organic extracts were then dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography to provide the desired aldehyde (10 mg, 100%). [α] 14.4° (c 0.5, $CHCl_3$); IR (neat): 1725, 1695, 1473, 1256, 1106, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.66 (d, 1H, J = 2.2 Hz), 3.91-3.93 (m, 2H), 3.19 (dq, 1H, J = 6.8, 9.2 Hz), 3.01-3.06 (m, 1H), 1.69-1.76 (m, 2H), 1.55-1.63 (m, 3H), 1.46-1.51 (m, 1H), 1.26-1.41 (m, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 1.03 (d, 3H, J = 6.7 Hz), 0.93 (s, 9H), 0.90 (d, 3H, J = 6.8 Hz), 0.88 (s, 9H), 0.11 (s, 3H), 0.064 (s, 3H), 0.041 (s, 3H), -0.034 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 215.0, 202.7, 79.0, 76.7, 53.6, 53.3, 48.8, 35.4, 29.7, 27.4, 26.3, 26.0, 25.3, 25.3, 25.0, 22.6, 19.2, 18.6, 18.4, 17.9, −3.2, −3.4, −3.6, −4.3. HRMS calculated for $C_{28}H_{56}O_4Si_2$ (M+Na): 535.3615; found: 535.3627.

To a solution of the aldehyde prepared above (10 mg, 0.02 mmol) in *t*BuOH (2.0 mL) and 2-methyl-2-butene (98 μL) was added a solution of $NaClO_2$ (2.5 mg, 0.03 mmol) in pH 3.5 aqueous phosphate buffer (0.39 mL) dropwise. The reaction was allowed to stir at room temperature for 30 minutes before partitioning the reaction mixture between distilled water and diethyl ether. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 10% to 20% ethyl acetate-petroleum ether to give the desired acid **25** (9 mg, 87%). [α] -4.4° (c 0.45, $CHCl_3$); IR (neat): 2500-3300, 1700, 1468, 1255, 1106, 837, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.94–3.97 (m, 2H), 3.25–3.33 (m, 2H), 1.87-1.94 (m, 1H), 1.72-1.78 (m, 1H), 1.65-1.70 (m, 2H), 1.55-1.61 (m, 2H), 1.38-1.49 (m, 2H), 1.34 (s, 3H), 1.31-1.34 (m, 1H), 1.19 (s, 3H), 1.08 (d, 3H, J = 6.5 Hz), 0.99 (s, 9H), 0.95 (d, 3H, J = 6.9 Hz), 0.94 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H), 0.092 (s, 3H), 0.080 (s, 3H) ; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 215.1, 182.2, 78.0, 79.5, 53.9, 49.0, 46.9, 35.2, 30.2, 29.2, 27.3, 26.3, 26.0, 25.5, 25.0, 21.4, 19.2, 18.6, 18.5, 18.0, −3.0, −3.3, −3.5, −4.2. HRMS calculated for $C_{28}H_{56}O_5Si_2$ (M+Na): 551.3564; found: 551.3556.

Ester 28: To a solution of acid **25** (4 mg, 7.6 μmol) in methylene chloride (0.3 mL) at room temperature was added DCC (2 mg, 9.8 μmol) followed by DMAP (1 mg, 9.8 μmol). To the reaction mixture was then added a

solution of thiazole alcohol **27** (2 mg, 9.1 μmol) in methylene chloride (0.2 mL) and the reaction allowed to continue stirring for 24 hours. The mixture was filtered through celite and washed with methylene chloride. The resulting solution was concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 2% to 10% ethyl acetate-petroleum ether to give the desired ester (3.7 mg, 66%). [α] -5.9° (c 0.18, $CHCl_3$); IR (neat): 1733, 1694, 1472, 1256, 1104, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.52 (s, 1H), 5.74 (dddd, 1H, J = 6.4, 6.4, 10.1, 16.8 Hz), 5.30 (dd, 1H, J = 5.7, 7.8 Hz), 5.13 (dd, 1H, J = 1.5, 17.0 Hz), 5.06 (dd, 1H, J = 1.6, 10.1 Hz), 3.89-3.91 (m, 2H), 3.22-3.28 (m, 2H), 2.69 (s, 3H), 2.54-2.60 (m, 1H), 2.45-2.50 (m, 1H), 2.13 (s, 3H), 1.80-1.84 (m, 1H), 1.59-1.72 (m, 3H), 1.23-1.46 (m, 5H), 1.20 (s, 3H), 1.10 (s, 3H), 1.01 (d, 3H, J = 6.7 Hz), 0.92 (s, 9H), 0.90 (s, 9H), 0.90 (d, 3H, J = 4.6 Hz), 0.095 (s, 3H), 0.069 (s, 3H), 0.042 (s, 3H), 0.019 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 215.4, 175.9, 164.7, 152.5, 136.7, 133.5, 121.3, 118.1, 116.6, 79.9, 79.8, 78.9, 54.1, 49.2, 47.0, 37.8, 34.9, 30.8, 29.0, 27.0, 26.3, 26.1, 25.7, 24.7, 21.5, 19.3, 19.3, 18.6, 18.5, 18.0, 14.6, –2.8, –3.2, –3.5, –4.2. HRMS calculated for $C_{39}H_{69}NO_5SSi_2$ (M+Na): 742.4333; found: 742.4330.

To a solution of the ester prepared above (3.7 mg, 5 μmol) in methylene chloride (0.5 mL) at 0°C was added TFA (0.1 mL) and the reaction allowed to stir at -12°C for four days. The reaction was then poured into cold, aqueous saturated sodium bicarbonate and extracted with chloroform. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 30% to 40% ethyl acetate-petroleum ether to give the desired dihydroxy ester **28** (1.9 mg, 77%). [α] -14.0° (c 0.1, $CHCl_3$); IR (neat): 3446, 1733, 1717, 1699, 1683, 1668, 1652, 1456, 1153, 968 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.50 (s, 1H), 5.73 (dddd, 1H, J = 6.9, 6.9, 10.1, 17.0 Hz), 5.34 (dd, 1H, J = 6.5, 6.5 Hz), 5.09 (dd, 1H, J = 1.5, 17.1 Hz), 5.04 (dd, 1H, J = <1, 10.3 Hz), 4.11 (d, 1H, J = 8.5 Hz), 3.96 (dd, 1H, J = 3.1, 8.4 Hz), 3.70 (d, 1H, J = 7.7 Hz), 3.21-3.27 (m, 1H), 2.68 (s, 3H), 2.44-2.55 (m, 3H), 1.78 (s, 3H), 1.77-1.84 (m, 3H), 1.59-1.66 (m, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.30 (d, 3H, J = 6.9 Hz), 1.21-1.26 (m, 4H), 1.00 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 223.1, 172.7, 164.6, 152.6, 137.1, 133.5, 120.6, 117.7, 116.3, 85.0, 78.4, 77.5, 49.1, 48.1, 47.5, 37.6, 34.8, 29.0, 28.9, 28.8, 27.7, 24.8, 22.0, 19.2, 18.9, 17.2, 14.8; HRMS calculated for $C_{27}H_{41}NO_5S$ (M+Na): 514.2603; found: 514.2601.

Ester 7: To a solution of acid **25** (5.4 mg, 0.01 mmol) in methylene chloride (0.3 mL) at room temperature was added DCC (3 mg, 0.01 mmol) followed by DMAP (2 mg, 0.01 mol). To the reaction mixture was then added a solution of thiazole alcohol **26** (2 mg, 0.01 mmol) in methylene chloride (0.2 mL) and the resulting mixture was allowed to stir for 24 hours. The mixture was filtered through celite, washed with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using a gradient of 2% to 10% ethyl acetate-petroleum ether to give the desired ester (6 mg, 87%). [α] -4.3° (c 0.3, $CHCl_3$); IR (neat): 1734, 1694, 1463, 1255, 1103, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.54 (s, 1H), 4.68 (d, 1H, J = 37.8 Hz), 4.65 (d, 1H, J = 38.3 Hz), 3.90-3.92 (m, 2H), 3.22-3.27 (m, 2H), 2.70 (s, 3H), 2.13 (s, 3H), 1.81-1.87 (m, 1H), 1.60-1.73 (m, 4H), 1.45-1.50 (m, 1H), 1.35-1.38 (m, 2H), 1.23-1.29 (m, 1H), 1.23 (s, 3H), 1.12 (s, 3H), 1.01 (d, 3H, J = 6.7 Hz), 0.93 (s, 9H), 0.88-0.90 (m, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.064 (s, 3H), 0.038 (s, 3H), 0.032 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 215.2, 176.8, 164.9, 152.4, 134.0, 121.9, 116.6, 80.0, 79.6, 77.2, 77.0, 76.7, 70.6, 53.9, 49.1, 47.2, 35.2, 30.5, 29.2, 27.2, 26.3, 26.1, 25.6, 25.1, 21.3, 19.3, 19.3,

18.6, 18.5, 18.0, 16.2, −2.9, −3.3, −3.5, −4.2. HRMS calculated for $C_{36}H_{65}NO_5SSi_2$ (M+Na): 702.4020; found: 702.4011.

To a solution of the ester prepared above (5 mg, 7.4 µmol) in methylene chloride (0.5 mL) at 0°C was added TFA (0.1 mL) and the reaction allowed to stir at -12°C for two days. The reaction was poured into cold, aqueous saturated sodium bicarbonate and extracted with chloroform. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 30% to 40% ethyl acetate-petroleum ether to give the desired diol **7** (2 mg, 60%). [α] -15.0° (c 0.1, $CHCl_3$); IR (neat): 3446, 1732, 1668, 1456, 1154, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.50 (s, 1H), 4.68 (d, 1H, *J* = 22.3 Hz), 4.65 (d, 1H, *J* = 22.3 Hz), 4.25 (d, 1H, *J* = 8.5 Hz), 4.00 (dd, 1H, *J* = 2.8, 8.5 Hz), 3.70 (d, 1H, *J* = 9.4 Hz), 3.25 (dq, 1H, *J* = 6.9, 8.7 Hz), 2.69 (s, 3H), 2.54-2.57 (m, 1H), 2.07 (s, 3H), 1.73-1.84 (m, 3H), 1.46-1.69 (m, 8H), 1.40 (s, 3H), 1.34 (s, 3H), 1.31 (d, 3H, *J* = 6.1 Hz), 1.00 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 223.2, 173.3, 164.7, 152.5, 134.5, 121.2, 116.3, 85.1, 77.4, 70.1, 48.9, 48.1, 47.5, 34.9, 29.2, 29.1, 28.8, 27.7, 24.7, 22.0, 19.2, 18.9, 17.2, 16.1. HRMS calculated for $C_{24}H_{37}NO_5S$ (M+Na): 474.2290; found: 474.2281.

Ester 32: 7-octenoic acid (60 mg, 0.42 mmol) was dissolved in 10 mL of CH_2Cl_2. DCC (90 mg, 0.55 mmol, 1.3 eq) and DMAP (54 mg, 0.55 mmol, 1.3 eq) were then added and after 10 minutes of stirring, alcohol (10 mg, 0.55 mmol, 1.2 eq) was introduced. The reaction mixture was then stirred for 24 hours at room temperature. Water (2 mL) was added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulting oil was purified by column chromatography using a 15% ethyl acetate-hexane to give pure ester as a white solid (108 mg, 70 %). [α] +2.1° (c 0.30, $CDCl_3$); mp = 123-124.5°C; IR (KBr pellet): 2930, 2857, 1710, 1684, 1534, 1458, 1220, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.49 (s, 1H), 5.72 (m, 2H), 5.30 (t, 1H, *J* = 6.51 Hz); 4.87-5.10 (m, 4H), 2.68 (s, 3H), 2.48 (t, 2H, J=7.39 Hz), 2.29 (t, 2H, *J* = 7.60 Hz), 2.02 (s, 3H), 1.12-1.74 (m, 5H), 0.83 (t, 3H, *J* = 6.24 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 150.1, 138.4, 131.0, 120.6, 117.6, 116.2, 114.3, 77.8, 57.0, 50.5, 37.6, 34.5, 33.5, 32.4, 30.4, 28.6, 25.8, 24.8. HRMS calculated for $C_{19}H_{27}NO_2S$ ($M+NH_4$): 351.2106; found: 351.2115.

Lactone 33 (E and Z): Ester **32** (10 mg, 0.03 mmol) was dissolved in 3 mL of dry CH_2Cl_2 and Ru-catalyst (2 mg) was added. The resulting mixture was then stirred for 24 hours at room temperature. Evaporation of volatiles and purification of the residue by column chromatography gave 8 mg (80 % yield) of mixture of E/Z isomers (1:1 ratio, determined by HPLC), which were separated by column chromatography chromatography using a 10% ethyl acetate-hexane

Z-isomer: [α] +61.6 (c 1.00, $CDCl_3$); . IR (neat): 2924, 2852, 1730, 1455, 1245, 1140 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.56 (s, 1H), 5.48 (d, 1H, *J* = 11.1 Hz), 5.46 (ddd, 1H, *J* = 15.6, 11.0, 2.8 Hz), 5.31 (dddd, 1H, *J* = 15.6, 10.6, 3.9, 1.8 Hz), 2.68 (s, 3H), 2.44 (m, 2H), 2.36 (m, 2H), 2.07 (s, 3H), 1.62-1.90 (m, 5H), 0.86-1.42 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 152.2, 137.4, 134.8, 126.4, 119.4, 115.9, 75.8, 38.4, 35.3, 34.2, 33.1, 29.6, 26.6, 25.7, 24.4, 19.2. HRMS calculated for $C_{17}H_{23}NO_2S$ (M+Na): 328.1347; found: 328.1337.

***E* isomer:** [α] +50.6 (c 1.00, $CDCl_3$); IR (neat): 2931, 2863, 1734, 1463, 1239, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.56 (s, 1H), 5.49 (m, 1H), 5.32 (dt, 1H, J=10.2, 3.6 Hz), 5.25 (d, J=1H, 10.4 Hz), 2.68 (s, 3H), 2.49 (m, 2H), 2.16 (m, 2H), 2.07 (s, 3H), 1.12-1.68 (m, 5H), 0.86-1.04 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 154.3, 138.3, 134.1, 125.9, 117.4, 116.1, 73.2, 37.9, 35.1, 34.2, 33.9, 30.2, 28.1, 26.2, 22.2, 19.9. HRMS calculated for $C_{17}H_{23}NO_2S$ (M+Na): 328.1347; found: 328.1332.

Epoxide 6 from Z-33: A solution of dimethyldioxirane (0.29 mL, 0.02 mmol, 0.07 M solution in acetone) was added dropwise to a cooled (-30 ^oC) solution of 5 mg (0.018 mmol) of alkene **Z-33** in 1 mL of dry CH_2Cl_2. After stirring for 3 hours, evaporation of volatiles and purification of the residue by column chromatography using a 15% ethyl acetate-hexane gave a mixture of inseparable diastereoisomeric epoxides (1:1 ratio, determined by HPLC) in 81 % yield (5 mg). [α] +15.3 (c 0.10, $CDCl_3$); IR (neat): 2922, 2850, 1733, 1558, 1456, 1238, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.95 (s, 2H), 6.54 (s, 2H), 5.48 (dd, 2H, *J* = 12, 2.5 Hz), 2.72 (m, 4H), 2.69 (s, 6H), 2.50 (m, 2H), 2.42 (m, 1H), 2.39 (m, 1H), 2.29 (m, 2H), 2.19 (m, 2H), 2.06 (s, 6H), 1.83 (m, 2H), 1.12-1.69 (m, 8H), 0.72-0.96 (m, 6H). HRMS calculated for $C_{17}H_{23}NO_3S$ (M+Na): 344.1296; found: 344.1305.

Epoxide 6 from E-33: A solution of dimethyldioxirane (0.28 mL, 0.02 mmol, 0.07 M solution in acetone) was added dropwise to a cooled (-30 ^oC) solution of 5 mg (0.018 mmol) of alkene **E-33** in 1 mL of dry CH_2Cl_2. After stirring for 3 hours, evaporation of volatiles and purification of the residue by column chromatography using a 15% ethyl acetate-hexane gave a mixture of inseparable diastereoisomeric epoxides (1:1 ratio, determined by HPLC) in 76 % yield (4.5 mg). [α] +12.6 (c 0.10, $CDCl_3$); IR (neat): 2935, 2864, 1732, 1562, 1455, 1237, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.95 (s, 2H), 6.54 (s, 2H), 5.48 (d, 2H, *J* = 10.8 Hz), 3.08 (m, 2H), 2.82 (m, 2H), 2.68 (s, 6H), 2.57 (m, 1H), 2.51 (m, 1H), 2.33 (m, 1H), 2.30 (m, 1H), 2.14 (m, 2H), 2.08 (s, 6H), 199 (m, 2H), 1.05-1.54 (m, 10H), 0.81-0.88 (m, 6H). HRMS calculated for $C_{17}H_{23}NO_3S$ (M+Na): 344.1296; found: 344.1289.

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